REMARKS

Claims 1-12 and 28-48 are pending in the application. Claims 13-27 were previously cancelled without prejudice or disclaimer. Claims 1 and 9 have been amended to incorporate the limitations of claim 2 and claims 10 and 34, respectively, solely in an effort to expedite the allowance of the application. Claims 2, 10 and 34 are hereby cancelled without prejudice or disclaimer. Since the subject matter of claims 2, 10 and 34 have already been examined, Applicants respectively submit that the instant amendments pose no additional search burden on the Examiner and these amendments should be entered as a matter of right. Applicants reserve the right to pursue previously claimed subject matter in one or more continuing applications.

Applicants acknowledge the Examiner's withdrawal of the Final Rejection (mailed March 19, 2008) in which the following rejections/objections were made:

(i) rejection of claims 1-12 and 28-48 under 35 U.S.C. § 103(a) over Kruetzer et al. [US2005/0074757A1] in view of Elbashir et al. [The EMBO Journal, 20(23), 2001],Klug et al. [European J. of Physiology, 441(6 Suppl): R205 (2001)], Brown et al. [WO 94/19493], Siddique et al. [Neurology, 47 (Suppl 2): S27-S35 (1996)], and Kunst et al. [Nature Genetics, 15: 91-94 (1997); and

(ii) objection to claim 5 under 37 CFR §1.75(c) as being of improper dependent form.

With respect to the newly applied rejections, Applicants respectfully request reconsideration and examination of this application and the timely allowance of the pending claims in view of the arguments presented below.

Claim Rejections -35 U.S.C. §103

(a) Rejection of claims 1-12 and 28-40

The Examiner has newly rejected claims 1-12 and 28-40 under 35 U.S.C. §103(a) in view of Tuschl et al. [US 2004/2059247A1], Elbashir et al. [The EMBO Journal, 20(23), 2001], Klug et al. [European J. of Physiology, 441(6 Suppl): R205 (2001)], Brown et al. [WO 94/19493], Siddique et al. [Neurology, 47 (Suppl 2): S27-S35 (1996)], and Kunst et al. [Nature Genetics, 15: 91-94 (1996)]. In particular, the Examiner states that "both Tuschl et al. and Elbashir et al. have taught that siRNA can discriminate and inhibit targets with as little as one nucleotide change" (page 5 of the Office Action).

Applicants respectfully traverse.

Applicants respectfully submit that Tuschl et al. and Elbashir et al. appear to describe the same ***gene-specific silencing experiment*** in which the same seven (7) siRNAs are tested for their ability to cleave a ***common luciferase reporter gene*** target in an *in vitro* RNAi cleavage assay (see, e.g., Fig. 8 of Elbashir et al. and Fig. 18 of Tuschl et al.). Of the 7 siRNAs, 6 siRNAs contain modified sequence segments or single base changes which result in decreased RNAi activity. Neither Tuschl et al. nor Elbashir et al. describe cleavage of a "mutant" target mRNA or the ability of an siRNA to discriminate between different target mRNAs, much less target mRNAs that differ in sequence by only a few nucleotides. One skilled in the art at the time of the invention would not have envisioned with any reasonable expectation of success that the mutant siRNAs of Tuschl et al. and/or Elbashir et al. would efficiently silence an intended target allele while leaving a non-target allele intact, and particularly when said target alleles differ by no more than a few nucleotides and where both alleles are present in the same cell or organism. Nothing in Tuschl et al. and/or Elbashir et al. teaches or suggests such allelic discrimination and, in particular, nothing in the cited references would lead to any reasonable expectation of success in achieving such discrimination.

Moreover, Applicants submit that whether single nucleotide specificity was achievable with RNAi technology had not been resolved by those of skill in the art at the time of the claimed invention. For example, as of Applicants' earliest priority date, there were several reports that RNAi technology could tolerate single-base mismatches between the antisense strand of the siRNAs and the target RNA. For example, Boutla *et al.* (Boutla A et al., *Current Biology*, 11: 1776-80; published Nov. 15, 2001 and previously made of record as reference C5 in the Information Disclosure Statement filed July 11, 2008) indicated that single nucleotide discrimination was beyond the limits of siRNA technology. Boutla *et al.* reported that siRNAs differing from the sequence of their target mRNA at one or more nucleotides retained efficacy, indicating that the siRNA technology did not require perfect sequence complementarity of the siRNA with the mRNA to silence its expression.

Furthermore, it should be noted that the claims have been amended herewith to specify that the mutant target allele comprises a mutation (e.g., a dominant gain-of-function mutation or point mutation) ***correlated with the neurodegenerative disorder***, and the claimed method

comprises administering to the cell an siRNA specific for the mutation such that allele-specific RNAi of the mutant target allele occurs and expression of the wild-type allele is preserved. Thus, to selectively silence the mutant allele correlated with a neurodegenerative disorder, single nucleotide specificity is required. However, at least one report published prior to the filing date of the application suggested that RNAi technology was incapable of selectively inhibiting the expression of a mutant allele correlated with a neurodegenerative disorder. For example, Caplen et al. (Caplen NJ et al., *Hum. Mol. Genet.,* 11: 175-84 (2002)) attempted to selectively inhibit the expression of mutant huntingtin protein (which causes Huntingtin's Disease) but was unsuccessful.

In view of the foregoing reports, one skilled in the art would have had no reasonable expectation that single-nucleotide discrimination would be successful to selectively inhibit the expression of a mutant allele correlated with a neurodegenerative disorder. In fact, based at least on Boutla et al. and Caplen et al., the skilled artisan would have expected that the wild-type allele would be silenced in addition to the mutant allele. Furthermore, there is nothing in Tuschl et al. or Elbashir et al. demonstrating that a wild type allele correlated with a neurodegenerative disorder (or any other wild-type allele) would be ***resistant to RNAi.*** Notably, the siRNA methodology of the instant invention significantly and selectively silences a target mutant gene corresponding to neurodegenerative disorder while leaving the corresponding wild type gene largely unaffected.

In summary, the Examiner has failed to point to any teaching in the cited references that would compel one of ordinary skill in the art to make the claimed invention ***with any reasonable expectation of success***. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and [b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). In view of the foregoing, Applicants request that the rejection of the claims under § 103(a) be reconsidered and withdrawn.

In view of the foregoing, Applicants request that the rejection of the claims 1-12 and 28-40 under § 103(a) be reconsidered and withdrawn.

(b) Rejection of claims 41-48

The Examiner has newly rejected claims 41-48 under 35 U.S.C. §103(a) in view of Tuschl et al. [US 2004/2059247A1], Elbashir et al. [The EMBO Journal, 20(23), 2001], Klug et al. [European J. of Physiology, 441(6 Suppl): R205 (2001)], Brown et al. [WO 94/19493], Siddique et al. [Neurology, 47 (Suppl 2): S27-S35 (1996)], and Kunst et al. [Nature Genetics, 15: 91-94 (1996)] as applied to claims 1-12 and 28-40 above, and further in view of Brummelkamp et al. [Science Express, March 21, 2002]. Here again the Examiner has relied on Tuschl et al. and Elbashir et al. as primary references for the §103 rejection. Without again addressing the alleged teachings in the cited references, Applicants submit that the rejection is improper for at least the same reasons given above with respect to the rejection of claims 1-12 and 28-40. Accordingly, reconsideration and withdrawal of this is also respectfully requested.

CONCLUSION

In view of the above amendment and response, Applicants believe the pending application is in condition for allowance. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney, Debra J. Milasincic, Esq., at (617) 227-7400.

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Respectfully submitted,

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